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Angelos A. Kambouris

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The Role of Major Hepatic Resections for Liver Metastases from Colorectal Cancer†

Angelos A. Kambouris, MD*

Of the more than 120,000 new patients with colorectal cancer in 1982 (1), at least 20% will develop liver metastases either at initial presentation or after treatment of the primary lesion. The median survival in such patients has been variously estimated at between five and nine months (2), and in spite of treatment by chemotherapeutic agents, only rarely do such patients survive five years (2,3). By contrast, patients who survive the longest after treatment of liver metastases from colorectal cancer have had major hepatic resections alone or combined with chemotherapy as part of their management (4-9). The present report describes five patients who were treated for liver metastases by anatomic hepatic lobectomy, either alone or combined with other treatment approaches.

Materials

Five patients have been treated by anatomic hepatic lobectomy by the author since 1978 (Table I). There were four men and one woman, ranging in age from 39 to 71 years. The rectum was the primary site in three patients, the sigmoid in one, and the descending colon in the fifth. While liver metastases were detected within six to 19 months after initial treatment in three patients, they were present at the time of diagnosis of the primary tumor in the remaining two. Three of the patients had undergone no treatment for liver metastases before hepatic resection was undertaken. One had been treated by means of hepatic artery infusion with 5-fluoro-2-deoxy-uridine (FUDR) for approximately 13 months, and his disease apparently stabilized. Hepatectomy was undertaken when he developed gradually rising carcinoembryonic antigen (CEA) in the absence of extrahepatic metastases. The last patient presented with advanced liver dysfunction due to metastases, markedly decreased performance status, jaundice, and weight loss. At the time of sigmoid resection for treatment of his primary cancer, the right hepatic artery was ligated, and the patient was treated by systemic chemotherapy.

No deaths resulted from hepatectomy in this small series, and only one patient developed a major complication, which delayed her discharge by approximately 12 days.

Case 1

A 47-year-old white man had undergone abdominoperineal resection for carcinoma of the rectum in September 1974. No metastases to the liver were found at operation. In June 1975, he developed hepatomegaly, and multiple liver metastases were detected by liver scan. After extrahepatic metastases were excluded, a catheter was surgically introduced into the hepatic artery in June 1975, and the patient was treated with continuous infusion of 5-FUDR (0.3 mg/kg/day) for about 13 months, by means of a Watkins chronofusor pump®. His disease stabilized, but treatment was interrupted because of catheter dysfunction. In 1977, he developed a splenic and left subphrenic abscess, attributed to the inlying hepatic artery catheter. Splenectomy and drainage of the abscess were carried out, and the catheter was removed. In January 1978, the CEA levels started to rise; a detailed evaluation over a five-month period showed no extrahepatic metastases. In May 1978, an anatomic right hepatic lobectomy was performed through a thoraco-abdominal incision for a multilobulated metastatic mass. He recovered from the operation well, and the CEA levels reverted to normal.

He remains asymptomatic four and a half years later, without further treatment. Although it is not possible to speculate on the course of his disease had resection not been performed, the fact that active carcinoma was found in the resected specimen, that the CEA levels have remained normal, and that the patient has remained

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*Department of Surgery, Division of General Surgery, Henry Ford Hospital
Address reprint requests to Dr. Kambouris, General Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

asymptomatic all strongly suggest the beneficial effect of operation.

Case 2

A 56-year-old white man underwent low anterior resection for carcinoma of the rectosigmoid colon in September 1978. At operation, a solitary metastases was found in the left lobe of the liver, adjacent to the falciform ligament. Upon oncological evaluation, he was advised against chemotherapy, since he had asymptomatic metastatic disease. The patient consented to left hepatic lobectomy after a six-month observation and reevaluation, during which time no extrahepatic disease developed. At operation in April 1979, a 6 cm lymph node was also removed from the supraduodenal region and was found to be replaced by metastatic adenocarcinoma.

The patient had an uneventful recovery and remained asymptomatic for twenty months without further treatment. He then developed regional recurrence with obstructive jaundice, which was treated with a percutaneously inserted biliary drainage catheter and systemic chemotherapy. His disease has remained stable for the last twenty months, although on several occasions he has been hospitalized for treatment of catheter obstruction and cholangitis. Although it would be impossible to predict the clinical course of this patient had he not undergone resection of his metastasis, one can assume that the disease process would have advanced, making subsequent treatment difficult.

Case 3

A 68-year-old white man had undergone abdominoperineal resection in December 1978 for carcinoma of the rectum. In June 1981, he presented with clinical and radiographic evidence of metastases to the right lobe of the liver. A thorough evaluation, including bone scans and pelvic radiographs for pain in the bony pelvis, failed to demonstrate metastases. After surgical and oncological evaluation, he underwent a right hepatic lobectomy for a large metastatic mass to the dome of the right lobe of the liver.

He was discharged on the 12th postoperative day after an uneventful recovery. However, his pelvic pain persisted, and in September 1981, three months after hepatectomy, he was found to have large pelvic bone metastases. In retrospect, in spite of the 18-month interval between the treatment of the primary carcinoma and the development of the liver metastases, this patient harbored extrahepatic disease at the time of hepatic resection. Bone pain had been the only clue to the existence of metastases, and bone scans were not helpful. For this patient, no long-term benefit was derived from major liver resection, although the operation at the time was based on sound principles.

Case 4

A 49-year-old white man was found to have a carcinoma of the sigmoid colon, in the course of diagnostic workup for massive right hepatic metastases, abnormal liver functions, weight loss, and markedly decreased performance status. The left lobe of the liver appeared normal on a liver scan, and no extrahepatic metastases were detected. A visceral angiogram showed a dual arterial supply to the liver: the right hepatic artery originated from the superior mesenteric, and the left lobe was supplied by the proper hepatic artery. The gastroduodenal artery was normal. A two-stage approach was planned, in view of the patient's diminished performance status and marked hepatic dysfunction. In April 1981, a sigmoid resection was performed; a tumor occupying about 80% of the right lobe of the liver was also biopsied, and a nodule in the lateral segment of the left lobe of the liver, which was found to be cancerous, was excised. The right hepatic artery was doubly ligated, and several enlarged, clinically malignant nodes in the supraduodenal region were biopsied; on permanent section, they were found to be benign, hyperplastic nodes. After three days of fever and increasing levels of hepatic enzymes, the patient steadily improved.

He had an uncomplicated postoperative course and was discharged on the 11th postoperative day. He was subsequently treated with systemic chemotherapy (5-FU) and improved dramatically. His liver functions returned to near normal levels, he gained weight, and his performance status returned to normal. In October 1981, through a thoracoabdominal incision, a right hepatic lobectomy and wedge resection of the lateral segment of the left lobe were carried out. Both specimens showed carcinoma, although there was necrosis in the central portion of the tumor of the right lobe. An effort to insert a catheter into the proper hepatic artery via the gastroduodenal artery for infusion chemotherapy was unsuccessful. After he was discharged from the hospital, chemotherapy was resumed and continues to date. The patient remains asymptomatic one year after hepatectomy.

Case 5

A 39-year-old white woman underwent left colectomy for carcinoma of the descending colon in April 1981. No liver metastases were found at operation. Six months later, while investigating her for rising CEA levels, we detected a large solitary metastasis on the dome of the right lobe of the liver. In January 1982, two days after

visceral arteriograms were obtained using the right femoral artery for catheter insertion, a right hepatic lobectomy was performed through a thoracoabdominal approach. On the fifth postoperative day, she developed right iliofemoral thrombophlebitis which required anticoagulant therapy and elastic support.

She was discharged on the 23rd postoperative day and remains on anticoagulant therapy. Although she has remained asymptomatic and has gained weight, nine months after hepatectomy, her CEA levels are currently rising. Despite no objective evidence of disease, it is presumed that she harbors metastases.

Discussion

The treatment of patients with liver metastases from colorectal cancer remains controversial. Hepatic resections for treatment of primary and metastatic tumors of the liver were introduced in the late 1800s. By 1899 Keen (10) was able to summarize 76 reported cases from the literature and to document a surgical mortality of 14.9% in 59 cases in which the procedure was adequately described. The same high mortality following major hepatic resections was documented by Lortat-Jacob and Robert in 1952 (11), Quattlebaum in 1953 (12), Pack and Baker in 1953 (13), Brunschwig in 1953 (14), and by Pack, Miller, and Brasfield in 1955 (15). The resurgence of interest in major hepatectomies in the 1950s was stimulated in part by Healey's description of the segmental anatomy of the liver in 1954 (16), and in part by the emphasis on more extended operations performed in efforts to control cancer. Adson and Beart summarized the historical background of major hepatic resections in 1977 (17).

The high surgical mortality after hepatic resection and the simultaneous discovery of multiple antineoplastic compounds in the 1950s, along with the ease of administration and the theoretical advantages of simultaneous treatment of multiple sites, diverted efforts from surgical to chemotherapeutic management of patients with liver metastases. Although systemic chemotherapy continues to play a role in 1982, its effectiveness in treating patients with liver metastases has remained low, with response rates averaging 20% (2,18), in spite of a variety of agents used alone or in combination. In efforts to improve the effectiveness of chemotherapy to the liver while avoiding systemic toxicity, Sullivan, et al (19) popularized prolonged hepatic intraarterial infusion chemotherapy, using a permanently inserted catheter into the hepatic artery and a portable external pump for continuous delivery of antimetabolites, usually FUDR. Infusion chemotherapy for primary as well as metastatic cancer to the liver has found a limited but definite acceptance as a treatment approach; it has facilitated the development of innovative combinations of drugs, isotopes, or concurrent use of radiation therapy. Its effectiveness has

TABLE I

Clinical and Operative Details in Patients Undergoing Hepatic Lobectomy for Metastases from Colorectal Cancers

No.	Age/ Sex	Primary Location	Primary Treatment	Interval to Metastases (mos)	Prior treatment of metastases	Procedure	Complications	Hospital stay Postoperative	Results	Comments
1	50, M	Rectum	A-P. resection Sept. 1974	8	Hepatic artery infusion for over 12 mos	Right hepatic lobectomy April 1978	None	19 days	Free of cancer Sept. 1982	Had splenectomy and drainage of subphrenic abscess March 1977
2	57, M	Rectum	Low anterior resection Sept. 1978	0	None	Left hepatic lobectomy excision of celiar l. nodes April 1979	None	10 days	Recurrence with jaundice Dec. 1980	On biliary drainage and chemotherapy Sept. 1982
3	71, M	Rectum	A-P. resection Dec. 1978	18	None	Right hepatic lobectomy June 1981	None	12 days	Pelvic bone metastases Sept. 1981	Bone scan and radiographs negative June 1981
4	49, M	Sigmoid colon	Sigmoid resection; right hepatic artery ligation; biopsy left lobe of liver and hilar nodes April 1982	0	Right hepatic artery ligation; chemotherapy (5-FU) for 6 mos	Right hepatic lobectomy; wedge excision nodule of left lobe of liver	None	11 days	Free of cancer Oct. 1982 On maintenance chemotherapy	Presented with massive liver metastases. Dramatic response to hepatic artery ligation and chemotherapy before hepatectomy
5	39, F	Descending colon	Left colectomy April 1981	6	None	Right hepatic lobectomy Jan. 1982	Iliofemoral thrombophlebitis	23 days	Asymptomatic rising CEA metastases suspected Sept. 1982	Thrombophlebitis at site of femoral artery puncture two days before hepatectomy

increased response rates to over 60%; and it has prolonged median survival in patients with metastases from colorectal cancers (2,5). Its role has recently been enhanced by the development of a totally implantable pump delivery system, obviating many of the pump and catheter-related complications (20). The effect of infusion chemotherapy, although it appears favorable, will require time for definite assessment.

Because of the lack of success of systemic chemotherapy and the promising but uncertain effectiveness of infusion chemotherapy, the interest in hepatic resections to treat liver metastases from colorectal cancer has been revived in the past ten years. Stimulating reports by Wilson and Adson in 1976 (4), followed by reports by others (2,4-9), and by refinements in surgical techniques as described by McBride (5) and Starzl (21), are primarily responsible. Adson, et al (9), in summarizing the Mayo Clinic experience in 1980, stated that 41% of 32 patients surviving hepatic resections lived three or more years, three patients were alive from 10 to 22 years, and 20-30% of all patients benefited from hepatic resection regardless of how long they survived. Similarly, Logan, et al (2) reported three of 19 patients who survived more than five years and one who survived eight years after major hepatic resection for metastases from colorectal cancer. The most comprehensive survey, however, was undertaken by Foster (7,8), who summarized the cases of more than four hundred patients undergoing hepatic resections for treatment of liver metastases. He calculated an overall surgical mortality of 11%, but the rate was only 6% for 125 patients operated for metastases from colorectal cancers. Among those who survived the operation, the five-year survival rate ranged from 19% to 26%. Patients with solitary metastases did better than those with multiple lesions, and the results were inversely affected by the extent of the operation. As a result of that review, Foster strongly recommends an aggressive approach to liver metastases from colorectal cancer, while surgical treatment of metastases from other organs should be approached on an individual basis.

The benefits of hepatectomy in our patients need to be evaluated on an individual basis also. There is little doubt that the first patient benefited from resection of the only known metastases. The fact that he remains asymptomatic four and a half years later with a normal CEA level justifies the rationale for the operation. Likewise, the fourth patient derived definite benefit from the hepatic artery ligation initially, the interval systemic chemotherapy, and the right hepatic lobectomy six months later. Whether the wedge excision of a solitary metastasis from the lateral segment of the left lobe will affect the clinical course remains to be seen. Lack of symptoms and normal performance status 12 months later attest to the effectiveness of operation so far. In the second patient, the effect of left hepatic lobectomy and excision of a large nodal metastasis would be impossible to ascertain. Although the patient remained totally asymptomatic for twenty months, he was asymptomatic at the time of operation also. The development of bony metastases only three months after hepatectomy in the third patient negates any benefits he might otherwise have derived. It is well known to clinicians that pelvic bony pain is a significant premonitor of recurrent or metastatic disease after abdomino-perineal resection for rectal cancers. Because of this suspicion, diagnostic work-up had been detailed but failed to detect preclinical metastases before hepatectomy. In the fifth patient, the benefit is obviously minimal as she developed abnormal CEA levels six months after hepatectomy, in spite of her excellent performance status. However, stem cell assay of the resected metastasis showed no effect of the commonly used chemotherapeutic agents in this patient, which indicates that using chemotherapy as an alternate to resectional treatment would likewise have failed. From that point of view, in addition to removing the only known metastasis at the time, the procedure afforded important information which might influence future management whenever metastases become recognized. The successful recovery of all five patients, the minimal postoperative hospital stay, and the lack of complications in four of the five make hepatic lobectomy attractive when compared to a less effective but definitely more symptomatic systemic chemotherapy.

Summary

Major hepatic resections have assumed an important role in treating liver metastases for colorectal cancers. They are particularly indicated for solitary or even clustered unilobar metastases, when the primary tumor has been controlled. The mortality rates of approximately 6% and the reported disease-free, five-year rates of over 20% indicate that such resections have become safe and are feasible under proper conditions.

Among our five patients undergoing hepatic lobectomy, there were no deaths and only one complication. One patient remains asymptomatic at four and a half years, one suffered a recurrence after twenty months, and the third developed bone metastases within three months of operation. The fourth patient remains asymptomatic at 12 months but is receiving maintenance chemotherapy; and the fifth, while asymptomatic, is suspected to harbor metastases nine months after hepatectomy.

This experience is too limited to allow conclusions on its own merits. However, it agrees with information in the surgical literature which justifies the consideration of heptic lobectomy for solitary liver metastases from colorectal cancer as an alternative to or in conjunction with systemic chemotherapy. Given the individual selection process in the reported surgical series, and the variety of nonresective therapeutic regimens, a controlled clinical trial would be the most objective mechanism to evaluate the efficacy of major hepatic resections for treating patients with liver metastases from colorectal cancer.

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